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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

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| PETER E. CROSS, GEOFFREY N. THOMAS and JOHN E. ARROWSMITH | | Art No. 129 |
| SERIAL NO.: | 07/044,086 | Examiner: R. COVINGTON |
| FILED: | APRIL 29, 1987 | |
| FOR: | "ANTIARRHYTHMIC AGENTS" | |
| OUR REF: | SPC 7068/A (PLC 428/A) | |

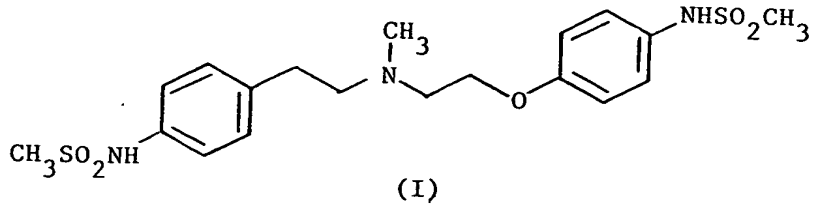
DECLARATION UNDER RULE 132

I, JOHN E. ARROWSMITH declare as follows;

1. I was awarded the degree of Bachelor of Science with Honours in Chemistry and the degree of Doctor of Philosophy from the University of East Anglia at Norwich. I am a member of the Society of Chemistry and Industry.

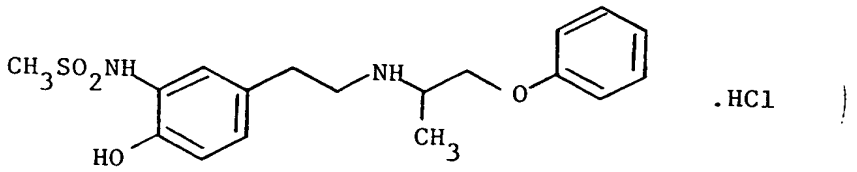
Between September 1979 and May 1989 I was employed by Pfizer Limited, Sandwich, Kent, England in the Discovery Research Department where I was a Team Leader responsible for the design and synthesis of medicinal compounds. Since May 1989 I have worked in the Project Planning Department of Clinical Research within the same company.

2. The subject U.S. application serial no. 07/044086 concerns compounds having Class III antiarrhythmic activity. The preferred embodiment of the invention is specifically claimed in claim 54 of the specification and has the following structure:-



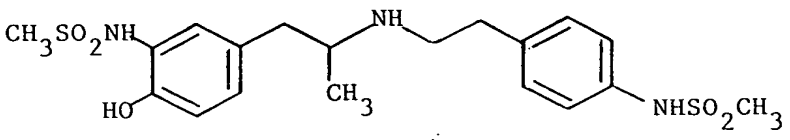
(I)

The closest "structural" prior art to the present invention is in my view US-A-3,574,741 (hereafter US'741), in particular the compounds of Examples 8 and 21 of this reference. These compounds are described as being sympathomimetic agents for use as nasal decongestants or as vasoconstrictors for the treatment of certain ophthalmic conditions. In other words they are <u>not</u> suggested as antiarrhythmic agents. The compounds of Examples 8 and 21 have the following structures:-



(II)

US'741, Example 8



(III)

US'741, Example 21

3. The compound of the formula (II), Example 8 of US'741, was prepared in the free base form as a hemihydrate by the route disclosed in the patent. I submitted this compound (free base form) to my colleagues in the Pharmacology Department at Pfizer Limited, Sandwich, Kent, England for comparison with the compound of the formula (I) of the present application in terms of its effects on the refractoriness and conduction time in guinea pig papillary muscle in vitro, using the general procedure set out on pages 16 and 17 of the present application.

The results obtained are presented in graphic form in Figures 1 and 2 hereafter and clearly show that the compound of the formula (I) of the present application increased the cardiac effective refractory period (ERP) in a dose dependent manner (dose range 5-1000 nM) without affecting the conduction time (CT) and so, by definition (see E. M. Vaughan Williams, J. Clin. Pharmacol., 24, 129 [1984]), the compound of the formula (I) of the present application is a Class III antiarrhythmic agent.

In contrast the compound of the formula (II) of US'741 had no effect on either the cardiac ERP or CT over a similar dose range (10-1000 nM) and so is definitely not a Class III antiarrhythmic agent.

Figure 1

Effect of Compound (I) and Compound (II) on refractoriness in guinea pig papillary muscle in vitro

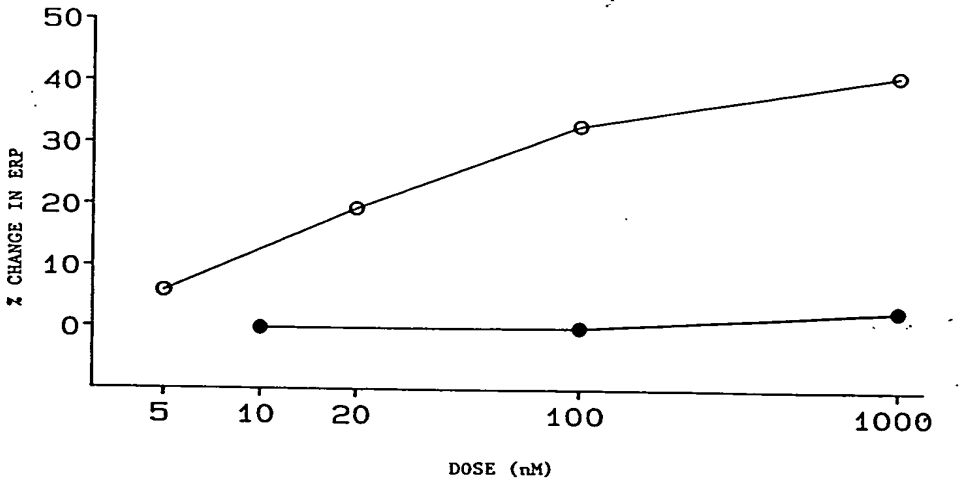
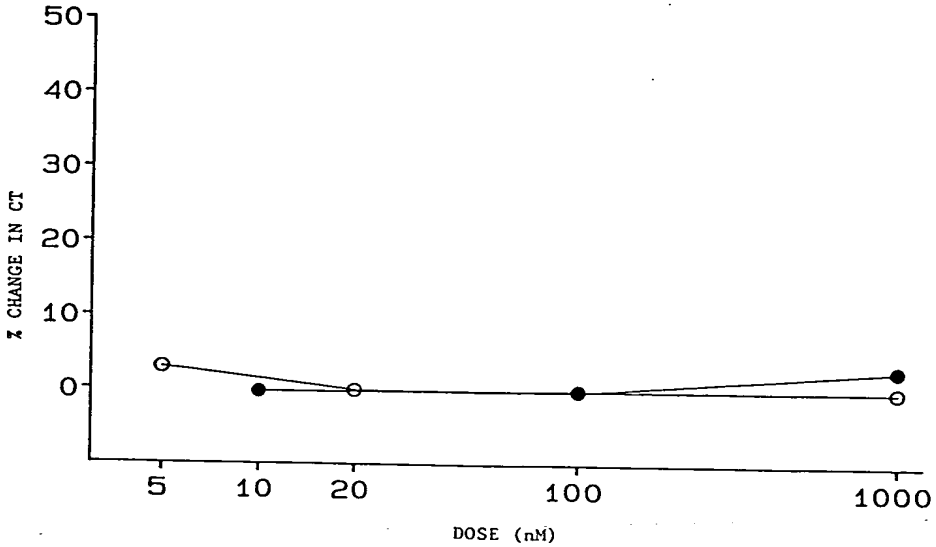



Figure 2

Effect of Compound (I) and Compound (II) on conduction time (CT) in guinea pig papillary muscle in vitro




—O— Compound (I) - mean of 5 experiments.

—●— Compound (II) - mean of 2 experiments.

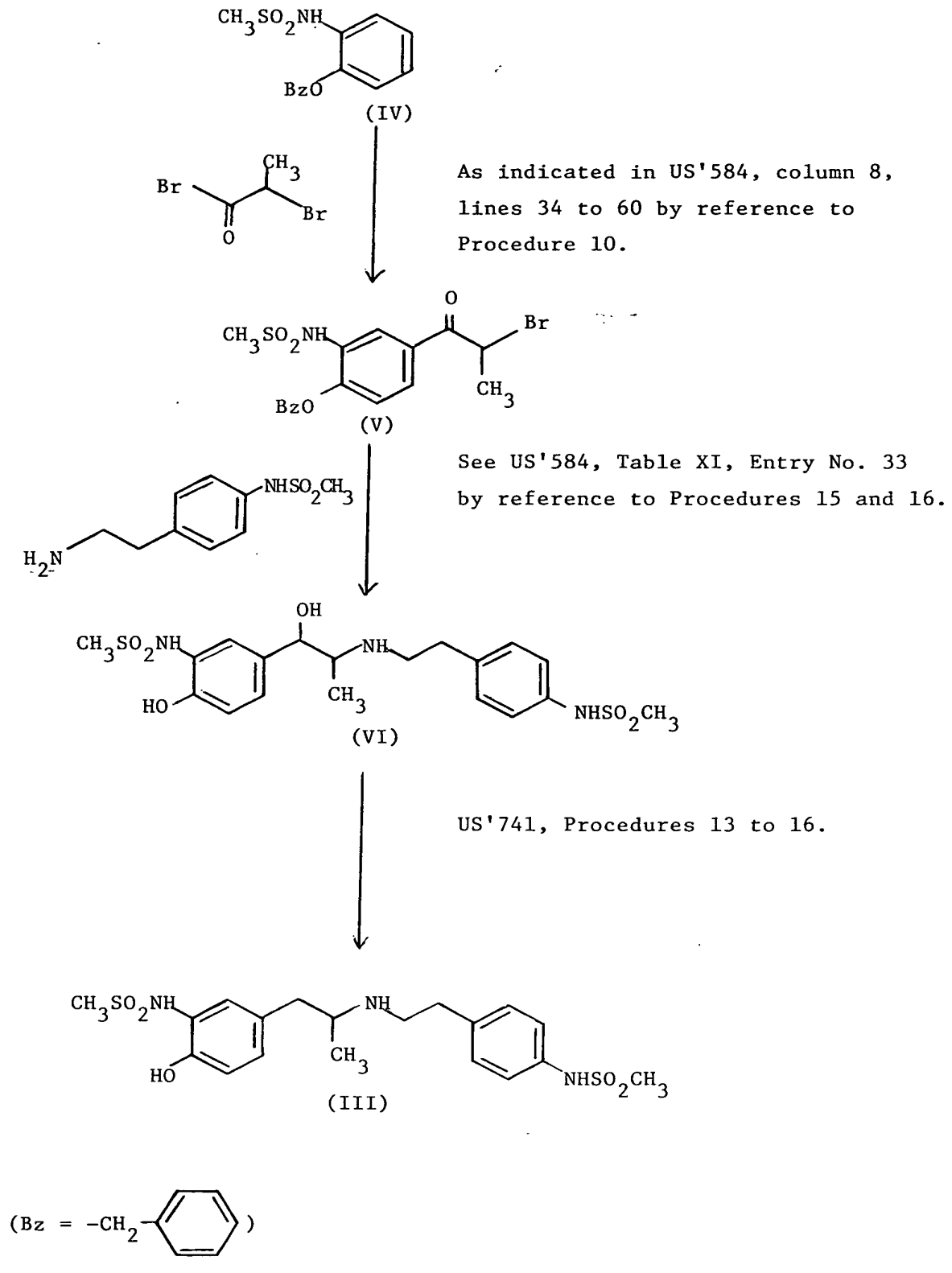
4. The compound of the formula (III), Example 21 of US'741, could not be prepared by the route disclosed in this patent and thus a similar comparative study could not be carried out for this compound.

The specific synthetic route to (III) is not immediately apparent on inspection of US'741. The intended preparative procedure is referred to in column 11 on lines 71 to 74, which is presumed to read on to the relevant list in column 13 on lines 1 to 15.

Accordingly the phenethylamine derivative (III) appears to have been prepared from the relevant phenethanolamine precursor described in Table XI (i.e. Entry no. 33) of US-3,341,584 (hereinafter US'584), by a method or methods disclosed in Procedures 13 to 16 of US'741.

Piecing together the information given the synthetic route to (III), based on the patent disclosure, appears to be as represented in Scheme 1 below:-

Scheme 1




(Bz = $-CH_2-C_6H_5$)

The synthesis failed since the named intermediate 2-benzyloxy-5-(2-bromopropionyl)methanesulphonanilide (compound (V) in Scheme 1) could not be prepared as described in US'584 (column 8, lines 34 to 60) using similar Friedel-Craft conditions to those specified in Procedure 10.

Procedure 10 of US'584 is stated to produce an analogous product in an isolated yield exceeding 90%. There is no indication that the conditions should be varied significantly for the preparation of (V).

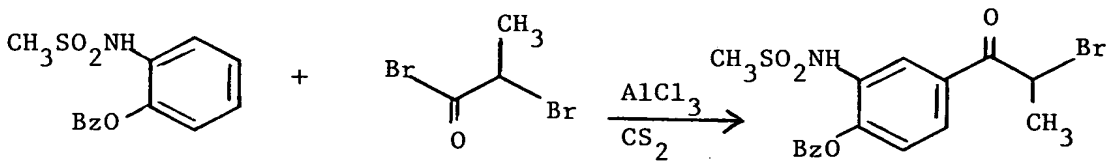
An attempt to prepare (V) by the disclosed procedure failed to yield the product in isolatable yield. The viscous oily layer obtained after decantation of the carbon disulphide solvent failed to yield a "solid" after acidic hydrolysis. TLC analysis of the oily product showed complete digestion of the starting material (IV) during the reaction with the formation of a multitude of products.

Two further experiments were carried out in which the reaction temperature was lowered in an attempt to reduce the incidence of by-product formation. In another experiment 1,1,2,2-tetrachloroethane was substituted for carbon disulphide as the reaction solvent. Attempts were made to separate and identify the products formed but this proved extremely difficult. No spectroscopic evidence was obtained for the formation of (V) in any of these procedures, let alone in isolatable yield.

Full details of these experiments are given in procedures 1 to 4 which follow:-

Procedure 1

Attempted Preparation of 2-benzyloxy-5-(2-bromopropionyl)-methanesulphonanilide




2-Benzyloxymethanesulphonanilide (0.50 g, 0.0018 mol) was dissolved in carbon disulphide (2 ml) at room temperature and treated with 2-bromopropionyl bromide (0.69 g, 0.33 ml, 0.0032 mol).

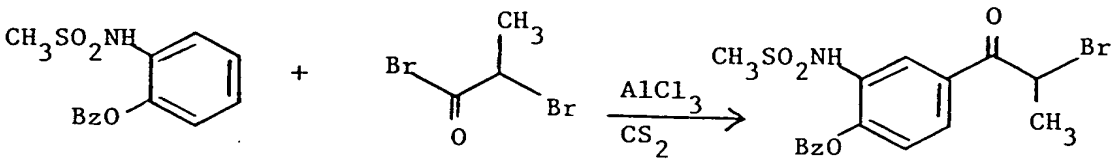
The reaction mixture was further stirred at room temperature under nitrogen and treated with aluminium chloride (0.72 g, 0.0054 mol) portionwise over 15 minutes. During the addition a red viscous phase formed. After the addition was complete the reaction was heated under reflux for 30 minutes. The two phases were miscible at this stage. The heat bath was then removed and stirring at room temperature was continued for 1.5 hours. The solvent was decanted from the viscous oil and

residue was treated with ice-water (3.73 ml) containing concentrated hydrochloric acid (0.13 ml). An exothermic reaction took place and therefore the reaction was cooled in ice-water. This gave an oil which was stirred for several minutes at room temperature. The product did not crystallize, therefore the solvent was decanted off and the oil/gum was stirred first with water, decanted, and then stirred with isopropanol/methanol. The product failed to crystallize.

An aliquot of the oil was dissolved in dichloromethane and evaluated by TLC. This showed no starting material remaining with the appearance of a multitude of products. Therefore the reaction was not further evaluated.

Procedure 2

Attempted preparation of 2-benzyloxy-5-(2-bromopropionyl)-methanesulphonanilide



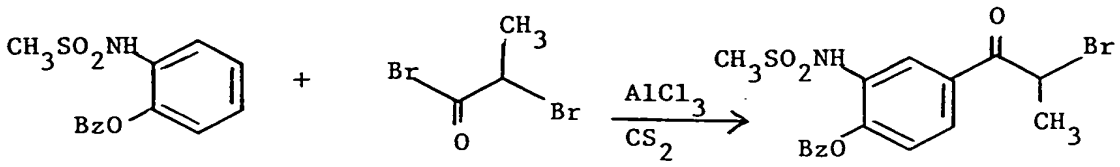
2-Benzyloxymethanesulphonanilide (0.50 g, 0.0018 mol) was dissolved in carbon disulphide (2 ml), cooled to 0°C with stirring under nitrogen and treated with 2-bromopropionyl bromide (0.69 g, 0.33 ml, 0.0032 mol) followed by aluminium chloride (0.72 g, 0.0054 mol), the latter portionwise over 30 minutes. The reaction mixture was stirred at 0°C for 30 minutes and then decanted to remove the carbon disulphide. The residue was spooned into ice-water (35 ml) containing concentrated hydrochloric acid (1.2 ml) to give a creamy gum. This was stirred for 1 hour in an attempt to induce crystallisation. However this did not occur therefore the mixture was extracted with ethyl acetate. The organic extracts were dried ($MgSO_4$) and concentrated under reduced pressure to give an oil. The oil was subjected to flash chromatography on a silica column (containing 30 g of silica) eluting with dichloromethane/methanol (99:1). Two main product fractions were obtained.

One fraction appeared to contain two compounds by TLC. The second fraction contained a product that lacked the benzyl group by N.M.R. analysis and this was discarded.

Separation of the two-component fraction was attempted by flash chromatography on silica eluting with dichloromethane/methanol (98:2). This was unsuccessful. Further TLC and HPLC analysis proved unable to separate the two products and the experiment was abandoned.

Procedure 3

Attempted preparation of 2-benzyloxy-5-(2-bromopropionyl)-methanesulphonanilide

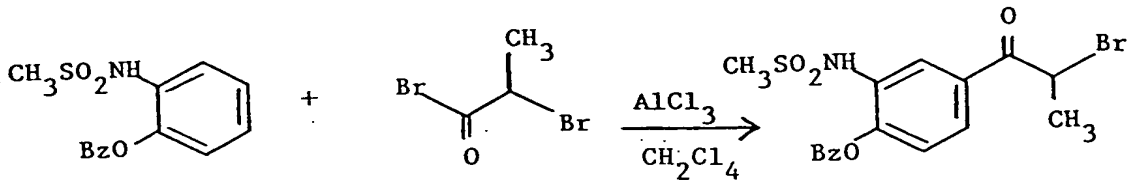



2-Benzyloxymethanesulphonanilide (0.50 g, 0.0018 mol) was dissolved in carbon disulphide (10 ml) under nitrogen and cooled to -78°C. The solution was treated with 2-bromopropionyl bromide (0.69 g, 0.33 ml, 0.0032 mol) followed portionwise by aluminium chloride (0.72 g, 0.0054 mol). Stirring was continued allowing the reaction temperature to rise until such a point that no starting material remained by TLC. The temperature at this point was about -30°C and ice-water (35 ml) containing concentrated hydrochloric acid (1.2 ml) was added to the mixture. The mixture was extracted with dichloromethane (2 x 125 ml), the combined extracts were washed with brine, dried ($MgSO_4$) and filtered.

TLC analysis of the organic extract showed no improvement over the reaction described in Procedure 2 and therefore the experiment was abandoned.

Procedure 4

Attempted preparation of 2-benzyloxy-5-(2-bromopropionyl)-methanesulphonanilide




2-Benzyloxymethanesulphonanilide (0.50 g, 0.0018 mol) was dissolved in 1,1,2,2-tetrachloroethane (10 ml) and the solution cooled to 0°C. 2-Bromopropionyl bromide (0.69 g, 0.33 ml, 0.0032 mol) was added followed by aluminium chloride (0.72 g, 0.0054 mol), the latter portionwise over 30 minutes. The red solution resulting was stirred at 0°C for 1 hour.

TLC analysis showed no starting materials remaining with the appearance of 4 products.

The reaction was poured into ice-water (35 ml) containing concentrated hydrochloric acid (1.2 ml). The mixture was extracted with dichloromethane (2 x 125 ml), the combined extracts washed with brine, dried ($MgSO_4$) and concentrated under reduced pressure to provide an oil.

TLC analysis of the oil showed no improvement over the reaction described in Procedure 2 and therefore the experiment was abandoned.

5. In summary, it has been shown that the preferred embodiment of the present invention, the compound of the formula (I), is a potent Class III antiarrhythmic agent.

In contrast, the compound of the formula (II), Example 8 of US'741, which is the structurally closest synthesisable prior art specifically disclosed in the literature, possesses no Class III antiarrhythmic activity.

Four attempts to prepare an intermediate necessary for the preparation of the compound of the formula (III), Example 21 of US'741, either by the route disclosed in the patent or by slight modifications thereof, were unsuccessful. Since this intermediate is not commercially available and no alternative routes have been disclosed thereto, no further experimentation was considered necessary in this regard.

6. All statements made herein of my knowledge are true and all statements made on information and belief are believed to be true. These statements are made with knowledge that wilful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and knowledge that wilful false statements may jeopardise the validity of the application or any patent issuing thereon.

21 December, 1989

Dr John E. Arrowsmith.

DR. JOHN E. ARROWSMITH